model SCA1 by inserting 175 expanded CAG repeats into one allele of the Atxn1 gene, producing mice expressing ATXN1 throughout the brain and displaying SCA1 symptoms. Previous research has indicated the role of localization of the ATXN1 protein to the nucleus in pathology. Therefore, the $Atxn1^{175QK772T/2Q}$ mouse model was created by disrupting the NLS in the expanded $Atxn1^{175Q/2Q}$ mice by replacing lysine with threonine at position 772 in the nuclear localization sequence (NLS). Since this amino acid change previously blocked PC disease in another mouse model, the $Atxn1^{175QK772T/2Q}$ mice were created to examine how the NLS mutation affects neuronal cells. RNA sequencing analysis was previously performed and found differentially expressed genes (DEG) with $Atxn1^{175Q/2Q}$ downregulated compared to $Atxn1^{175QK772T/2Q}$ and $Atxn1^{2Q/2Q}$ in the cerebellum, medulla, cortex, hippocampus, and striatum. The aim was to analyze these brain regions to validate the RNAseq differential gene expression at a protein level.

Participants and Methods: Therefore, western blots were performed on the following mouse models (n=12): wild type mice ($Atxn1^{2Q/2Q}$), mice with the nuclear localization sequence mutation ($Atxn1^{2QK772T/2Q}$), and mice with 175 expanded CAG repeats ($Atxn1^{175/2Q}$). Based off the RNAseq data, the cerebellum was tested with ion channel genes (Cav3.1, Kcnma1, and Trpc3) and the striatum was tested with a gene found in medium-spiny neurons (DARPP-32).

Results: In the cerebellum, $Atxn1^{175/2Q}$ was significantly downregulated compared to $Atxn1^{175QK772T/2Q}$ in Cav3.1, Trpc3, and Kcnma1. Atxn1$^{175Q/2Q}$ was significantly downregulated compared to $Atxn1^{2Q/2Q}$ in Trpc3 and Kcnma1. $Atxn1^{175QK772T/2Q}$ was significantly downregulated compared to $Atxn1^{2Q/2Q}$ in Trpc3. In the striatum, there was significantly reduced DARPP-32 expression found between $Atxn1^{2Q/2Q}$ and $Atxn1^{175QK772T/2Q}$, $Atxn1^{2Q/2Q}$ and $Atxn1^{175Q/2Q}$, and $Atxn1^{175Q/2Q}$ and $Atxn1^{175QK772T/2Q}$.

Conclusions: Therefore, the significantly reduced gene expression at the protein level in the cerebellum and striatum validate RNAseq differentially expressed genes. Additionally, the downregulation of both the $Atxn1^{175Q/2Q}$ and $Atxn1^{175QK772TQ/2Q}$ compared to $Atxn1^{2Q/2Q}$ in the striatum supports the lack of learning of those mouse models on the rotarod, suggesting that the nuclear localization mutation does not rescue learning. Interestingly, the downregulation of $Atxn1^{175Q/2Q}$ compared to $Atxn1^{175QK772TQ/2Q}$ likely supports the age-related motor decline rescue in the rotarod seen in $Atxn1^{175QK772T/2Q}$ and not $Atxn1^{175Q/2Q}$.

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61 Factors Affecting Executive Functioning in Patients with Parkinson's Disease

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Objective: Parkinson's disease (PD) is one of the most prevalent neurodegenerative conditions that leads to progressive degeneration in areas of the brain that control movement. As the disease progresses, cognition is also frequently affected, primarily executive functioning. Multiple factors may be involved in the relationship between PD and cognitive dysfunction. This study seeks to determine the association between disease duration (i.e., years since PD diagnosis), vascular comorbidities, and cognitive reserve (CR) and their relationship with executive functioning, in a clinic-referred PD population.

Participants and Methods: Participants included English-speaking subjects with a diagnosis of PD made by the patient's treating neurologist (i.e., movement disorders specialist) who received their neurological care and had undergone a comprehensive neuropsychological evaluation at Thomas Jefferson University Hospital in Philadelphia, PA over the past five years. The sample consists of 67 patients. Comprehensive medical and psychiatric histories were obtained, and individuals with severe psychopathology (e.g., bipolar disorder or schizophrenia), medical or other neurological disorders (e.g., seizure disorder, stroke, documented head injury that was more severe than a mild TBI or intracranial bleeding) that could account entirely for cognitive impairment were excluded. An overall domain score of executive functioning was calculated by averaging each participant's T-scores for the individual neuropsychological tests. Regression

analysis was utilized to explore the relationship between number of vascular comorbidities, disease duration, and CR, as measured by a composite of formal education and literacy level, with executive functioning performance on neuropsychological testing for this sample.

Results: The model explains 12.1% of the variance of executive functioning performance (F (3, 66) = 2.883, p = 0.043). A significant positive relationship was found between CR and executive functioning (b = .335, p = 0.008). No significant relationships were found between vascular comorbidities or disease duration with executive functioning. The relationship between CR and each neuropsychological measure was explored independently using Pearson correlation (2-tailed). Significant positive correlations were found between CR and WAIS-IV or WASI-II Similarities (r = .49, p < .001), CR and WAIS-IV or WASI-II Matrix Reasoning (r = .46, p = .001), and CR and FAS (r = .26, p = .037). No significant relationships were found between CR and TMT-B (r = .07, p = .565) or CR and Stroop Color and Word Interference (r = .17, p = .240).

Conclusions: Results suggest that CR may be a better predictor of executive functioning in patients with PD than number of vascular comorbidities or disease duration. Stronger premorbid cognitive functioning and better cognitive efficiency may be neuroprotective and stave off cognitive decline in Parkinson's disease.

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Keyword 1: Parkinson's disease
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62 Prediction of Mild Cognitive Impairment Conversion Using Cox Model in Parkinson's Disease

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Objective: Mild cognitive impairment (MCI) in Parkinson's disease (PD) is a critical state to consider. In fact, PD patients with MCI are more likely to develop dementia than the general population. Thus, identifying the risk factors for developing MCI in patients with PD could help with disease prevention. We aim to use the Cox regression model to identify the variables involved in the development of MCI in healthy controls (HC) and in a PD cohort.

Participants and Methods: The Parkinson's Progressive Markers Initiative (PPMI) database was used to analyze data from 166 HC and 365 patients with PD. They were analyzed longitudinally, at baseline and at 3-year follow up. Both HC and PD were further divided in 2 groups based on the presence or absence of MCI. Conversion to MCI was defined as the first detection of MCI. For all participants, we extracted the (1) Neuropsychiatric symptoms (anxiety, impulsive-compulsive disorders and sleep impairment), (2) 3T MRI-based data (cortical and subcortical brain volumes based on the Desikan atlas, using FreeSurfer 7.1.1) and (3) genetic markers (MAPT and APOE ε4 genes). We used Python 3.9 to perform three Cox proportional hazard models (PD-HC, HC only and PD only) and to model the risk of conversion to MCI, attributable to neuropsychiatric symptoms and cortical brain parameters. We included as covariates: age, sex, education, and disease duration (for the PD group). Hazard ratios (HRs) along with their 95% confidence intervals (CIs) are reported.

Results: When including both HC and PD in the model, Cox regression analyses showed that age of onset, diagnosis, the State-Trait Anxiety Inventory (STAI) and sleep impairment are variables that are associated with a greater risk of conversion to MCI (p<.005). For HC, only the STAI and the genetic marker MAPT were significantly associated with a risk of cognitive decline (p<.05). These results further indicated that a greater anxiety score at the STAI leads to a greater chance of developing a MCI whereas being a carrier of the MAPT gene reduces the risk of MCI. Regarding analysis on PD, results revealed that the STAI and the cortical volumes of the frontal dorsolateral and temporal regions are involved with a greater risk of developing a MCI (p<.05).

Conclusions: These analyses show that the neuropsychiatric symptom of anxiety seem to play an important role in the development of a MCI (significant in all three analyses). For patients with PD, cortical volumes of the frontal dorsolateral and temporal regions are significantly related to risk of MCI. This study